Synthesis and Antimicrobial Activity of Some New *N*-(Substituted phenyl)-*N*'-[2,3-dihydro-2-oxido-3-(4'-fluorophenyl)-1*H*-(1,3,2)benzoxazaphosphorin 2-yl]ureas

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Substituted benzoxazaphosphorin 2-yl ureas were synthesized by reacting 2-(4-fluoro-phenylamino)methylphenol (4) with different carbamidophosphoric acid dichlorides (3) in the presence of triethylamine in dry toluene at 45-50 °C and characterized by spectral data. These compounds were found to possess good antimicrobial activity.

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INTRODUCTION

Organophosphorus compounds being ubiquitous in nature have found multifaceted applications. Phosphorous heterocycles substituted with carbamate moieties are important classes of antitumour agents [1], pesticides [2], and bactericides [3,4]. Substituted phosphoryl ureas of the type RR'P(O)NHCONR" R''' possessed pesticidal activity [5-7]. In view of this, several *N*-(substitutedphenyl)-*N*'-[2,3-dihydro-2-oxido-3-(4'-fluorophenyl)-1*H*-(1,3,2)benzoxazaphosphorin 2-yl]ureas have been synthesised, expecting them to possess a broad spectrum of biological activity. Compounds were characterised by elemental, IR, NMR and Mass spectral analyses.

RESULTS AND DISCUSSION

The synthetic route (Scheme 1) involves the addition of dichloroisocyanatophosphine oxide [1,8] (1) with various

amines (2a-i) at -15° C under inert anhydrous conditions in dry toluene to afford the corresponding carbamidophosphoric acid dichlorides [9,10] (3a-i). After the addition of amines to 1, the products separated from the reaction mixture immediately as crystalline compounds. Further purification of 3a-i could not be accomplished due to their insolubility in many organic solvents and air sensitivity. Hence they were reacted directly *in situ* with a solution of 2-(4-fluoro- phenylamino)methylphenol (4) in toluene in the presence of two equivalents of triethylamine to yield 5a-i and their structures are established by IR, NMR and Mass spectral data (Table 1, 2, 3 and 4).

The ³¹P NMR spectral data for **5a**-**i** are given in Table 1. The ³¹P NMR signals [11] for **5a**, **5b** and **5f** appeared as two distinct signals in the range of -1.94 to -3.99 and -3.01 to -8.80 ppm, which may be due to the presence of two isomers in the solution state. The other compounds





5c-5e and **5g-5i** gave only one 31 P NMR signal in the region -1.42 to -8.48 ppm.

The ¹³C NMR chemical shifts (Table 3) for C-4 to C-10, C-1' to C-6' and C-1" to C-6" were observed in the expected range in the title compounds [12,13]. However, the signals for the carbon of the carbamido function appeared at δ 161.94-153.00. Signals for the remaining carbon atoms were observed in the expected regions. The ¹³C NMR chemical shifts could not be identified for **5h** and **5i** because of poor quality of their spectrum due to their meager solubility in DMSO.

In the proton NMR (Table 2), the aromatic protons of **5a-i** resonated as complex multiplets slightly downfield (δ 7.87-6.63) when compared to those of the starting compound **4** (δ 7.20-6.49) due to the deshielding effect of benzoxazaphosphorin 2-oxide ring. The C-4 methylene protons resonated as multiplets at δ 5.15-4.10 indicating their non-equivalence and coupling with phosphorus in the six-membered chair conformation of the benzoxazaphosphorin 2-oxide system [13]. The signal of phosphorylamidic proton of P(O)-NH-C(O) appeared much farther downfield, δ 8.72-8.16 when compared to that of carbamidic proton

 Table 1

 Synthetic and Analytical Data of N-(Substituted)-N-[2,3-dihydro-2-oxido-3-(4'-fluorophenyl)-1H-(1,3,2)benz-oxazaphosphorin 2-yl]ureas (5a-i)

Compd.	mp (°C)	Yield	Molecular	Elen Fou	nental ana Ind (Calco	ılysis 1)%		IR(cm ⁻¹)		³¹ P NMR	
	(0)	(70)	101 mula	С	Н	Ν	P=O	C=0	P-NH		
5a	241-243	71	$C_{20}H_{17}N_3PO_3F$	60.62	4.32	10.61	1270	1663	3262	-3 11 -8 80	
				(60.46	4.31	10.58)				-5.11, -0.00	
5b	142-144	68	C20H16N3PO3FCl	55.84	3.72	9.76	1269	1661	3279	1.04 2.01	
				(55.63	3.73	9.73)				-1.94, -3.01	
5c	147-149	62	C ₂₀ H ₁₆ N ₃ PO ₃ FBr	50.25	3.38	8.85	1272	1669	3261	200	
				(50.44	3.39	8.82)				-2.00	
5d	163-165	60	$C_{21}H_{19}N_3PO_3F$	61.52	4.67	10.17	1246	1656	3212	0 10	
				(61.31	4.66	10.21)				-0.48	
5e	146-148	63	$C_{22}H_{21}N_3PO_3F$	61.88	4.96	9.91	1274	1669	3267	2.14	
				(62.12	4.98	9.88)				-3.14	
5f	144-146	66	C ₂₁ H ₁₈ N ₃ PO ₃ FCl	56.37	4.08	9.46	1262	1671	3261	2.00 (17	
				(56.58	4.07	9.43)				-3.99, -6.17	
5g	131-133	64	$C_{21}H_{19}N_3PO_4F$	59.22	4.50	9.86	1271	1670	3263	2.00	
0				(59.02	4.48	9.83)				-2.80	
5h	179-181	70	C ₂₀ H ₂₃ N ₃ PO ₃ F	59.75	5.73	10.46	1273	1664	3271	1.42	
				(59.55	5.75	10.42)				-1.43	
5i	94-96	58	$C_{18}H_{19}N_3PO_4F$	55.43	4.86	10.77	1266	1668	3274	1.40	
			10 17 5 - 4	(55.25	4.89	10.74)				-1.42	

Table 2

¹H NMR Spectral data [a,b] of N-(Substituted)-N'-[2,3-dihydro-2-oxido-3-(4'-fluorophenyl)-1H-(1,3,2) benzoxazaphosphorin 2-yl]ureas (5a-i)

Compd.	Ar-H	-CH ₂ -	-NHC(0)	C(O)NH-	Alkyl-H
5a	7.87-7.13 (m, 12H)	4.32-4.15(m, 2H)	8.62	5.21	-
5b	7.71-7.10(m, 11H)	4.28-4.12(m, 2H)	8.52	5.90	-
5c	7.52-6.63(m, 11H)	4.29-4.20(m, 2H)	8.72	5.41	-
5d	7.41-6.69(m, 10H)	5.15-4.56(m, 2H)	-	4.21	2.06(s, 3H, CH ₃)
5e	7.81-7.04(m, 11H)	4.52-4.26(m, 2H)	8.71	5.10	2.91(s, 6H, 2CH ₃)
5f	7.61-6.99(m, 11H)	4.29-4.17(m, 2H)	8.16	5.27	4.04(s, 2H, -CH ₂ -)
5g	7.23-6.84(m, 11H)	4.23-4.13(m, 2H)	8.32	5.71	4.10(s, 3H, OCH ₃)
5h	7.73-7.20(m, 11H)	4.23-4.10(m, 2H)	8.64	5.60	1.92-1.52(m, 11H)
5 i	7.61-6.87(m, 7H)	4.42-4.20(m, 2H)	8.18	5.25	3.14-3.09(m, 4H, 3"&5"CH ₂) 3.05-2.99(m, 4H, 2"&6"CH ₂)

[a] Recorded in DMSO-d₆; [b] Chemical shifts in ppm.

Table 3

¹³C NMR Spectral data [a-c] of N-(Substituted)-N-[2,3-dihydro-2-oxido-3-(4'-fluoro phenyl)-1H-(1,3,2)benzoxazaphosphorin 2-yl]ureas (5a-i)

Carbon	5a	5b	5c	5d	5e	5f	5g
C-4	50.3	49.2	51.3	53.0	50.4	50.3	50.7
			(7.9)	(8.2)	(8.0)		(8.2)
C-5	127.4	127.1	130.4	129.2	128.9	129.1	128.4
C-6	122.8	120.9	122.4	120.4	122.2	120.1	120.3
C-7	129.2	129.9	127.1	126.9	127.7	126.4	128.4
C-8	121.3	120.0	118.7	119.9	117.7	116.4	114.0
C-9	156.6	154.8	149.2	150.3	-	-	-
	(7.5)	(7.2)	(7.6)				
C-10	129.8	127.2	124.5	122.8	123.7	122.8	124.7
C1′	129.1	128.1	134.1	138.0	130.9	-	143.4
	(6.9)				(6.8)		

C(O)-NH-R at, δ 5.90-4.21. Absence of splitting in signals for the protons of substituents (R) attached to the carbamido moiety shows that phosphorus coupling is limited to P-NH proton only [12].

The mass spectral data for 5d and 5h are given in Table 4. 5d Showed its molecular ion at m/z 411 with 99.9 percent abundance showing that the benzoxazaphosphorin ring is quite stable under electron impact. Presence of

Carbon	5a	5b	5c	5d	5e	5f	5g
C-2′	120.4	120.7	119.7	119.7	118.8	116.6	116.6
C-3′	119.3	119.1	122.3	123.9	-	120.1	120.3
C-4′	131.4	144.5	149.1	159.5	-	-	-
C-5′	120.9	121.0	118.6	119.0	116.8	116.7	117.0
C-6′	128.8	128.1	115.5	124.4	114.9	113.9	114.0
C-1''	130.8	138.2	149.2	133.2	-	-	-
C-2''	128.6	129.0	118.6	125.0	117.1	-	117.0
C-3''	126.1	127.1	128.7	126.5	116.3	116.6	106.4
C-4''	143.3	127.2	126.3	131.3	142.1	-	106.4
C-5''	124.6	123.5	128.6	116.2	121.0	-	117.1
C-6''	123.2	125.0	115.4	116.0	-	-	-
<u>C</u> =0	158.9	156.1	153.0	161.9	156.2	158.7	159.2
Alkyl	-	-	-	15.8	26.2	29.8	30.1
-					27.9		

Table 3 (Continued)

[a] Chemical shifts in ppm; [b] Recorded in DMSO-d₆; [c] J in Hz in Parentheses.

Table 4

Mass Spectral Data of some N-(Substituted)-N-[2,3-dihydro-2-oxido-3-(4'-fluorophenyl)-1H-(1,3,2) benzoxazaphosphorin 2-yl]ureas (5a-i)

Compd.	m/z (% relative abundance)	
5d	411[99.9, (M ⁺⁺)], 323(10), 306(7.5), 278(100), 187 (27.5).	
5h	403 [100, (M*)], 331 (17.5), 298 (22.5), 278(65.5), 187 (34.5).	

Table 5

Antifungal and Antibacterial Activities of Compounds 5 in Terms of Zone of Inhibition (mm)

Compd.		Fungi						Bacteria						
compu.	Aspergillus niger			Helmint	Helminthosporium oryzae			Escherichia coli			Staphylococcus aureus			
	100	50	25	100	50	25	100	50	25	100	50	25		
5a	8	-	-	10	6	-	9	5	-	9	4	-		
5b	12	7	3	12	9	4	10	8	3	10	8	5		
5c	13	6	3	12	7	-	11	8	3	12	7	4		
5d	11	7	-	10	8	-	10	7	-	10	6	3		
5e	10	7	2	10	6	2	-	-	-	10	8	-		
5f	11	7	3	11	8	-	10	5	-	10	8	4		
5g	13	11	-	12	7	-	12	8	-	10	7	-		
5h	10	7	3	11	6	2	8	5	-	8	5	-		
5i	13	8	3	12	8	2	-	-	-	11	8	5		
Bavistin	8	5	-	12	9	-								
Streptomycin							10	6	-	9	5	-		

Concentrations expressed in ppm; '-' indicates no activity.

 $(M^{**}-C_7H_4^{*})^+$ at m/z 323(10), $(M^{**}-C_7H_5O^{*})^+$ at m/z 306(7.5), base peak ion $(M^{**}-C_7H_7ON^{*})^+$ at m/z 278(100) conclusively confirms the proposed structure for **5d** and subsequently other members of this series.

The infrared spectra of **5a-i** (Table 1) exhibited stretching frequencies in the region 1246-1274 cm⁻¹, 3213-3279 cm⁻¹ and 1656-1671 cm⁻¹ for P=O [14,15], P-NH [12,16] and C=O [13,17] respectively.

EXPERIMENTAL

Dichloroisocyanatophosphine oxide (1). A suspension of phosphorus pentachloride (41.70 g, 0.2 mole) in dry 1,2-dichloroethane (100 mL) was placed into a three-necked round bottomed flask (500 mL) provided with a thermometer and an air condenser. The latter was connected to hydrogen chloride absorption tower. The mixture was cooled to 0° C and the suspension of urethane (17.80 g, 0.2 mole) in 1,2-dichloroethane

(100 mL) was added to it in small portions over a period of 20 minutes with occasional swirling of the reaction mixture. Evolution of ethyl chloride and hydrogen chloride gases started almost instantaneously. After evolution of gases subsided, the mixture was stirred with magnetic stirrer and slowly heated to reflux temperature and was maintained under reflux for 30 minutes. The apparatus, after flushing with dry nitrogen, was cooled to room temperature and refrigerated overnight. The solution was treated with charcoal, filtered and concentrated in the flash evaporator at 40°C. The residue on distillation under reduced pressure gave 27.6 g (75%) of **1** as colorless liquid, bp $36-37^{\circ}C/8 \text{ mm } [8]$.

Preparation of substituted phenyl carbamidophosphoric acid dichlorides (4). A solution of substituted anilines (2a-i, 0.005 mole) in dry toluene (30 mL) was added drop wise to a stirred cold solution (-15° C) of dichloroisocyanatophosphine oxide (1, 0.80 g, 0.005 mole) in dry toluene (40 mL). After the addition, the temperature of the reaction mixture was maintained in between -15° C to -5° C for 30 minutes. Later the temperature of the mixture was raised to room temperature and stirring was continued for another 30 minutes. Aryl carbamidophosphoric acid dichlorides (4a-i) were collected by filtration and dried under reduced pressure [18].

of N-(aryl)-N'-[2,3-dihydro-2-oxido-3-(4'-Synthesis fluorophenyl)-1*H*-(1,3,2)benzox-azaphosphorin 2-yl]ureas (5a-i). A solution of substituted phenyl carbamidophosphoric acid dichlorides (3a-i, 0.002 mole) in dry toluene (20 mL) was added to the solution of 2-(4-fluoro phenylamino)methylphenol (4, 0.43 g, 0.002 mole) and triethylamine (0.404 g, 0.004 mole) in dry toluene (20 mL) at 0°C. After the addition, the temperature of the reaction mixture was maintained at 0°C for one hour and then the temperature of the mixture was allowed to rise slowly to 45-50°C and stirring was continued for an additional five hours. The reaction progress was monitored by TLC in the 1:2 mixtures of ethyl acetate and hexane as a mobile solvent and silica gel as adsorbent. Triethylamine hydrochloride was separated by filtration and the solvent from the filtrate was evaporated under reduced pressure. The residue obtained after washing with water was dried and triturated with hot methanol to afford pure compounds (5a-i).

Antimicrobial Activity. The compounds **5a-i** (Table 5) were screened by Disc diffusion method [19,20,21] for their antimicrobial activity against the fungi, *Aspergillus niger & Helminthosporium oryzae* and bacteria, *Escherichia coli & Staphylococcus aureus* by comparing with standard fungicide Bavestein and standard bacteria Streptomycin at three different concentrations (25, 50, 100 ppm).

Compounds **5b-d**, and **5f** showed greater antimicrobial activity than that of the standard. However **5g** showed about one

and a half time greater antibacterial activity against *Escherichia coli* than that of standard. These results open up the possibility of their commercial applications as potent antimicrobials.

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